Pharmacokinetics

METABOLISM (BIOTRANSFORMATION) OF DRUGS

Learning objectives

- Define metabolism of drugs
- State the three possible fates of drugs after absorption
- State the two major ways in which metabolism changes drugs
- Discuss how metabolism reduces lipid solubility
- Discuss how metabolism alters biological activity of a drug
- State the reactions that bring about metabolic changes
- Describe the two phases of metabolism

Definition

- Metabolism is the process of chemical alteration of drugs in the body.
- i.e. the chemical alterations that occur to the drug within the body.

Fate of drugs after absorption

- The three possible fates of drugs after absorption are:

1. They could be metabolized by enzymes
2. They could change spontaneously into other substances without the intervention of enzymes
3. They could be excreted unchanged.

Ways in which metabolism changes drugs

- The processes of metabolism change drugs in two major ways:
  1. By reducing lipid solubility
  2. By altering biological activity

Reducing lipid solubility

- Metabolic reactions tend to make a drug molecule more water-soluble and so favour its elimination in the urine.
- Drug metabolism often converts lipophilic chemical compounds into more readily excreted hydrophilic products.
- Products of lipid soluble drugs are thus more water soluble and more readily excreted by the kidneys.

Altered biological activity

- Drugs are metabolized by enzymes with resultant:
  - Activation
  - Inactivation
  - Modification
- The end result of metabolism is the abolition of biological activity.

Altered biological activity

- Steps in drug metabolism:

1. Conversion of a pharmacologically active to an inactive substance. This applies to most drugs.
2. Conversion of a pharmacologically active to another active substance. This has the effect of prolonging drug action.
3. Conversion of a pharmacologically inactive to an active substance, i.e. prodrugs.

Organs of metabolism

- The liver is the most important organ for drug metabolism.
- Other tissues also contribute:
  - Kidneys
  - Gut mucosa
  - Lungs
  - Skin
  - Plasma

Organs of metabolism…

- The liver has special drug metabolizing enzyme system. Therefore:
- In liver disease drugs may be poorly metabolized, hence drug excretion is reduced.
- In a diseased liver, use of drugs may aggravate the illness.
- In neonates the liver microsomal enzyme system that metabolizes drugs is poorly developed and thus drug metabolism is slow, hence excretion is slower than in adults.

Reactions that bring about metabolic changes (biotransformation reactions)

NON-SYNTHETIC REACTIONS

1. Oxidation
2. Reduction
3. Hydrolysis
4. Cyclization
5. Decyclization

SYNTHETIC REACTIONS

1. Glucuronide conjugation
2. Acetylation
3. Methylation
4. Sulphate conjugation
5. Glycine conjugation
6. Glutathione conjugation
7. Ribonucleoside/nucleotide synthesis

Non-synthetic reactions

Oxidation:

- Involves addition of oxygen/ negatively charged radical or removal of hydrogen / positively charged radical.
- Oxidations are the most important drug metabolizing reactions
- Oxidation results in loss of electrons from the drug.
- Oxidation reactions include:
  - Hydroxylation
  - Oxygenation at C, N or S atoms
  - N- or O-dealkylation
  - Oxidative deamination

Non-synthetic reactions

Reduction:

- This is the converse of oxidation (and involves cytochrome P-450 enzymes working in opposite direction)
- Cytochrome P450 enzymes are housed in the smooth endoplasmic reticulum of the cell.

Hydrolysis:

- This is cleavage of drug molecule by taking up a molecule of water.
- Hydrolysis occurs in liver, intestines, plasma and other tissues.

Non-synthetic reactions

Cyclization:

- This is formation of ring structure from a straight chain compound. E.g. proguanil.

Decyclization:

- This is opening up of ring structure of the cyclic drug molecule, e.g. barbiturates and phenytoin.

Synthetic reactions

- These involve conjugation of the drug or its phase I metabolite with an endogenous substrate, to form a polar, highly ionized organic acid, which is easily excreted in urine or bile.
- Conjugation reactions have high energy requirement.

Synthetic reactions

Glucuronide conjugation:

- This is the most important synthetic reaction.
- Occurs in the hepatocyte cytoplasm
- The attachment of an ionized group makes the metabolite more water soluble.
- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose. E.g. chloramphenicol, aspirin, morphine, metronidazole.

Synthetic reactions

Acetylation:

- Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A. e.g.
  - Sulphonamides
  - Isoniazid
  - Paraaminosalicylic acid
  - hydralazine

Synthetic reactions

Methylation:

- The amines and phenols can be methylated. E.g. adrenaline, histamine.

Sulphate conjugation:

- The phenolic compounds and steroids are sulfated by sulfokinases. E.g. chloramphenicol, adrenal and sex steroids.

Phases of metabolism

- There are two phases of metabolism:
  1. **Phase I metabolism**
     - Nonsynthetic reactions
  2. **Phase II metabolism**
     - Synthetic/ conjugation reactions

Phase I metabolism

- This phase brings about a change in the drug molecule by oxidation, reduction or hydrolysis.
- Oxidation, reduction and hydrolysis introduce polar groups such as hydroxyl, amino, carboxyl into drugs, which are consequently made water-soluble, and pharmacologically less active.

Phase I metabolism…

- The new metabolite may retain biological activity but have different pharmacokinetic properties, e.g. a shorter half-life.
- The most important single group of reactions is oxidation, in particular those undertaken by the so-called **mixed-function (microsomal) oxidases.** These are capable of metabolizing a variety of compounds.

Phase I metabolism…

- Phase I oxidation of some drugs results in formation of **epoxides**, which are short-lived and highly reactive metabolites.
- Epoxides are important because they can bind irreversibly through covalent bonds to cell constituents; indeed this is one of the principal ways in which drugs are toxic to body tissues.
- **Glutathione** is a tripeptide that combines with epoxides, rendering them inactive. Its presence in the liver is part of an important defense mechanism against hepatic damage by halothane and paracetamol.

Phase II metabolism

- This involves union of the drug with one of several polar endogenous molecules to form a water-soluble conjugate which is readily eliminated by the kidney or if the molecular weight exceeds 300, in bile.
- Morphine, paracetamol and salicylates form conjugates with glucuronic acid.
- Oral contraceptive steroids form sulphates
- Isoniazid, phenelzine and dapsone are acetylated.
- Phase II metabolism almost invariably terminates biological activity.

Enzyme induction

- Enzyme induction is a process by which enzyme activity is enhanced, usually because of increased enzyme synthesis (or, less often, reduced enzyme degradation).
- The capacity of the body to metabolize drugs can be altered by certain medicinal drugs themselves or other substances that induce enzyme activity.
- These stimulate the microsomal enzyme systems (enzyme induction) accelerating biotransformation of drugs.

Enzyme induction…

Relevance of Enzyme induction to drug therapy:

- *Clinically important drug reactions may result*, e.g. failure of oral contraceptives or loss of anticoagulant control.
- *Disease may result*; e.g. antiepilepsy drugs increase the breakdown of dietary and endogenously formed vitamin D, producing an inactive metabolite – in effect vitamin D deficiency state, which can result in osteomalacia.
  - The accompanying hypocalcemia can increase the tendency to fits and a convulsion may lead to fracture of the demineralized bones.

Enzyme induction…

Relevance of enzyme induction…

- *Tolerance to drug therapy* may result in and provide an explanation for sub-optimal treatment, e.g. with an antiepilepsy drug.
- *Variability in response to drugs*: enzyme induction caused by heavy alcohol drinking or heavy smoking may be an unrecognized cause for failure of an individual to achieve the expected response to a normal dose of a drug.

Enzyme induction…

Relevance of enzyme induction…

- *Drug toxicity may be more likely*. A patient who becomes enzyme-induced by taking rifampicin is more likely to develop liver toxicity after paracetamol overdose by increased production of a hepatotoxic metabolite.

Substances that cause enzyme induction

- Barbiturates
- Barbequed meats
- Carbamazepine
- Ethanol
- Griseofulvin
- Phenytoin
- Rifampicin
- Tobacco smoke

Enzyme inhibition

- Some drugs inhibit enzyme activity thereby inhibiting metabolism of other drugs.
- Consequences of inhibiting drug metabolism can be more profound than those of enzyme induction.
- Enzyme inhibition is more selective and offers more scope for therapy.

Examples of enzyme inhibition

- Acetazolamide inhibits carbonic anhydrase and is used for the treatment of glaucoma.
- Allopurinol inhibits xanthine oxidase and is used for the tretment of gout.
- Disulfiram inhibits aldehyde dehydrogenase and is used for treatment of alcoholism.
- Enalapril inhibits angiotensin-converting enzyme and is used for treatment of hypertension and cardiac failure.

Thanks.

The end.